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Nutrition and the Formation of Urinary Calculi

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Nutrition and the Formation of Urinary Calculi

William H. Boyce, M.D.

Abnormal, usually roundish, stony deposits in the urinary tract are among the most ancient afflictions of man. They are known to have occurred as long as 8,000 years ago.[14] Judging from the incidence in current animals, calculi probably bedeviled the earliest mammalian kidneys.

No race or geographic area has been entirely free of the painful and often fatal disease, urinary calculi. There is general agreement that the incidence is greatest in southern China (Canton area), the Punjab district of India, northern Thailand, Arabia, and Mesopotamia (Iraq).[31, 26] Calculi are not uncommon in Holland, the east coast of Britain, the east and southeast of France, and the Balkan peninsula. In Africa stones are more common in the lower Nile region of Egypt. The greatest incidence in America occurs in the southeastern United States.[8] These "stone belts" are located near or between the Tropic of Cancer and 40 degrees north latitude. The incidence appears greatest near the Tropic of Cancer and decreases in frequency among Hindus, Arabs, southern Chinese, Siamese, and Europeans. No soil type, geologic substrata, or mineral content of either water or diet has been found to be common to these areas. With the possible exception of Madagascar, there are no corresponding "stone belts" along the Tropic of Capricorn.

Seasonal variations in the incidence of calculi have been reported in the United States, the increase beginning in early spring and reaching a maximum in late summer.[44] Prolonged periods of increased incidence of urinary calculi have produced reports of "stone waves."[22]

These geographic and seasonal variations are, at best, generalizations. The exact incidence of urinary calculi has not been determined even in America.[8]

The basic mechanisms of calculus formation remain unknown, although many systemic as well as localized genito-urinary diseases are recognized as predisposing factors.[19, 11] The recent review by Boshamer[6] emphasizes the failure of investigators to recognize the complexities of structure and composition of calculi. Oversimplification of the problem has limited the scope of research. Preventive therapy has been based largely on observation and experience and has been proportionately ineffectual.

I. STRUCTURE AND COMPOSITION OF URINARY CALCULI

The matrix. Both organic and inorganic components are present in the matrix, a part of all calculi. The archetypal matrix is a mucoid. Its approximate composition is: proteid, 65 per cent; glucide, 14 per cent; "bound water," 10 per cent and "bound inorganic ash," 12 per cent. The proteid part contains at least 18 amino acids. The glucide part contains glucose, galactose, mannose, rhamnose,

fucose, deoxypentose, and hexosamine.[34, 35] The "bound ash" is a mixture of inorganic substances with calcium and phosphorus present in all matrices, even when the major crystalline composition is cystine or uric acid. Trace amounts of serum proteins are present in the matrix of most calculi. These serum proteins are readily soluble in appropriate buffers so apparently represent adsorbates which contribute little to the mass or structural stability of the matrix.

The overall composition of the matrices from urinary calculi of various crystalline composition is sufficiently similar to suggest a common precursor. The substance in urine most likely to serve as a precursor is uromucoid. This relatively insoluble mucoid is present in all human urine, but is quantitatively increased in the urine of patients who are actively forming calculi. The amino acid and glucide components of normal uromucoid are those found in stone matrix. The differences between stone matrix and uromucoid are primarily in the relative quantities of the glucide monomers. "Sialic acid" is inconstantly present in normal uromucoid but is regularly absent from all calculous matrix.

Since "sialic acid" is usually a terminal unit of the glucide part of such molecules, its apparent lability with regard to uromucoid may indicate the frequent presence of glucosidases (neuraminidase) in human urine. Thus, such neuraminidase activity may be the first step in conversion of uromucoid to calcifiable stone matrix. Similarly, the remaining glucide parts of matrix are those found in uromucoid, but in reduced and variable relative concentration. The variation is always in the nature of a *reduction* of these components from the quantity present in normal uromucoid.[35] This fact implies that uromucoid is partially degraded by loss of glucide prior to or during stone formation. If this degradation is effected by more than one enzyme system, one might anticipate some degree of variation in the extent of the process and hence in the glucide content of various matrices. Such variation has been observed. The results are compatible with a degradation of uromucoid rather than the addition of some other agent to uromucoid. Many enzymes, including glucosidases, are present in normal urine; other enzymes may result from bacterial metabolism. Indeed, uromucoid recovered from the urine of patients with *B. proteus* infection may contain glucide compounds quantitatively more similar to stone matrix than to normal uromucoids or to uromucoid from calculous disease patients who were not actively forming calculi.[13] Whether these variations in glucide or in other as yet unkown structural variations of uromucoid are specific determinants of crystalline composition of calculi still remains to be elucidated.

The origin of uromucoid is unknown. Engfeldt has suggested that stone matrix is formed from microsomes of the renal tubular epithelium. He has presented electron microscopic evidence that parathyroid extract influences this process.[17] Grimes has suggested that some mucosubstance of blood plasma (mobilized bone matrix) is absorbed by the tubular cells and then excreted by them as a calcifiable matrix.[21] Immunochemical studies in our laboratories have suggested that normal uromucoid and stone matrix are antigenically the same substance. Neither uromucoid nor stone matrix was found to have antigenic

counterparts either in normal human blood plasma or in the plasma of the patients from whom the calculi were removed.[5] Whatever the origin of stone matrix may be, the kidney provides some indispensable factor or influence. Calculi cannot be produced in pouches of bladder mucosa which are isolated from the urinary stream even though adequate concentrations of calcium and phosphorus are available for calcification.[48]

The crystals of calculi. Although we have encountered a rare matrix calculus which contained practically no crystalline material, no purely crystalline stone without matrix has been discovered. The organic substances of crystalline structure reported to occur in calculi include uric acid, traces of urates, cystine, and xanthine. Approximately four per cent of renal calculi are uric acid, one per cent is cystine, whereas only 28 xanthine calculi have been reported in humans. Fully 95 per cent of renal calculi contain significant quantities of calcigerous crystals. Basic calcium phosphate (apatite) is present in 76 per cent, calcium oxalate in 52 per cent, and magnesium ammonium phosphate in 30 per cent.[36] The crystalline components are usually mixtures, a single type being encountered in less than ten per cent of all calculi.

II. FACTORS RELATED TO CALCULUS FORMATION

A. Matrix Formation

The mucoid matrix appears to be the one essential component of all stones.[9] The origin of matrix or its precursor(s) is unknown. Current theories include: (1) bone matrix which is transported in the plasma, filtered at the glomerulus, reabsorbed by the proximal tubular epithelium where it is reconstituted as a calcifiable matrix, and excreted in the urine;[21] (2) a product of renal tubular epithelial secretion;[17] (3) depolymerized renal tubular ground substance,[4] and (4) a secretory product of transitional or collecting tubular epithelium.[12] In its final form, matrix is not present in the blood plasma or in the secretion from transitional epithelium which has been isolated from the urine. Hence the renal tubular epithelium appears to be responsible for an essential component or alteration of the precursor of matrix. The influence of nutrition on matrix formation remains a *completely unexplored field.*

B. Crystal Formation

1. *Increase in urinary crystalloids* has received much attention as an etiologic factor in calculus formation. Patients with the most severe forms of calculous disease have a greater incidence of hypercalcinuria than do normal individuals from the same populations.[27, 7] This increase in calcium excretion is frequently associated with an increased volume of urine; hence the unit-volume concentration is not as different from the normal as is the 24-hour excretion rate. There is much evidence that hypercalcinuria may be contributory to calculus growth but that it is not *per se* an initiating cause of calculi.[10]

Urinary phosphorus excretion is within the normal range in the majority of patients with calculi.[7, 10] Oxalate excretion is rarely abnormal in patients with oxalate calculi unless they are victims of the rare "oxalosis syndrome."[15, 40] Uric acid calculi are not limited to patients with clinical gout. In fact, calcigerous calculi appear to be more common in patients with gout than in the population as a whole. Even in classical cystinuria, members of a family with essentially the same rate of cystine excretion exhibit wide variations in their tendency to calculus formation. Many dietary measures for prevention of calculi have been devised *a priori* from the chemical analysis of the crystalline content of the calculus recovered from the individual patient.[1] Such diets are designed to reduce the oral intake of the major crystalline components of the stone.

Low calcium diets have been supplemented with sodium phytate, which forms an unabsorbable complex with ionized calcium.[7, 25] Although moderate to marked reduction in urinary calcium regularly occurs in patients maintained on this regimen, the clinical indications and limitations in prevention of calculi remain to be established. There are no direct methods for determining whether increased intestinal absorption of calcium is *primary*, and hence not essential to metabolic balance, or whether it is *secondary* to alterations of body calcium by mobilization, transport, or excretory mechanisms. Certain patients appear to benefit from the low calcium routine, but the diagnosis of "idiopathic" hypercalcinuria is derived by the tedious and often dubious process of exclusion of known causes of hypercalcinuria.

Shorr recommended low phosphorus diets supplemented with basic aluminum gels which form insoluble complexes with intestinal phosphate.[46] This regimen has had extensive clinical application with reports of successful prevention of recurrence of calculi.[47, 37] Constipation and the monotony of the diet have made the regimen unpopular with patients. However, it is particularly recommended for those who have advanced impairment of renal function and who may have a tendency to retention of phosphate. Therapeutic efficacy is difficult to evaluate in view of the clinical observation that patients in renal insufficiency commonly cease to form calculi. Increase in urinary phosphate *per se* seems to have little influence on stone formation since patients receiving sodium phytate excrete two to three times the normal amount of urinary phosphorus without an increased tendency to calculus formation.

Diets low in oxalate have been recommended for patients with oxalate calculi.[26] There is no conclusive evidence that these patients have true hyperoxaluria or that the diets result in any appreciable reduction in urinary oxalate.[40]

The low purine diet with alkalinization of the urine and maintenance of maximal urine volume has been regularly utilized in patients with "pure" uric acid calculi. There are reports of *in vivo* dissolution of uric acid calculi by this program of management.[3] Such reports based on indirect data obtained from roentgenograms are equivocal, and many urologists have observed the formation of calcium phosphate or oxalate calculi in gouty patients on this regimen. Never-

theless, this remains the program of choice in management of patients with uric acid calculi.

All of these restrictive dietary measures have in common a high rate of failure to prevent recurrent calculus formation. The physician who has employed them with regularity is quite familiar with the incredulous expression of the many patients who reply, "But, Doctor, I have *never* eaten the forbidden items on this diet list!"

2. *Decrease in urinary "solubilizers"* of crystalline components of calculi has been a popular etiological concept of calculus formation. The suggested solubilizers have included urea, citrate, magnesium, amino acids, and "colloids." Howard[29] has recently revived this concept with an ingenious series of experiments involving the calcifiability of rachitic cartilage in urine. Calcifiable cartilage tends to calcify in the urine of patients who are potential stone formers, but not in the urine of normal persons. The essential mechanisms remain to be clarified, since cartilaginous enzymes, as well as urinary "solubilizers," may be implicated.

The state of equilibrium with regard to calcium concentration of urine has been studied by establishing new equilibria against ion-exchange columns,[18] against dialysates,[50] and various solid states.[2] Variations in calcium equilibria existing in voided urine as related to any of these standards are interpretable only as an indication that the activity coefficient of urinary calcium is more important than molar concentrations in determining calcium precipitability.

3. *Local factors* conducive to stone formation in the urinary passages include the presence of foreign bodies, stasis of urine, and infection. Bacteria which contain urease and thus produce a low urinary pH are common in patients with large renal calculi. It has been the prevailing opinion that infection is more commonly secondary to preexisting calculi than an initiating factor in their formation.[41] The role of active and healed infections in calculus formation may be revised as the diagnostic techniques for demonstrating the presence of urinary infections are improved.[43]

4. *Systemic diseases* associated with a high incidence of urinary calculi include hereditary, glandular, degenerative, metabolic, and malignant disturbances of body physiology.[11] The nutritional status of such patients is certainly abnormal, but the relationship to calculus formation is imponderable. These disease states are commonly accompanied by an increase in the urinary crystalloids which appear in calculi. Thus, calcium excretion is increased in hyperparathyroidism, Cushing's hyperadrenalism syndrome, sarcoidosis, and metastatic osteolytic cancers in which calcigerous calculi appear. Uric acid excretion is increased in gout and remissions of leukemias, in which uric acid calculi appear. That ambient conditions existing in the urine are important in determining the type of crystal is unquestioned.[12] That these same conditions are solely responsible for *calculus formation* is very much in question. The propensity of the kidney in these systemic diseases to form stone matrix is unknown.

III. RELATION OF DIET TO "IDIOPATHIC" CALCULUS FORMATION

Fully 85 per cent of all patients who form urinary calculi have no recognized local or systemic disease.[10] The role of diet has been inextricably linked with speculations as to the etiology of such calculi. Unfortunately, the available data are drawn from generalizations as to food habits of populations which exhibit either an exceptionally high or low incidence of urinary calculi. Correlations from such data may be useful in planning investigations of the problem and in preventing assumptions from achieving the status of worthy conclusions.

A. Dietary Surfeit of Urinary Crystalloids

Diets containing an excess of calcium, phosphate, oxalate, or purines have never been established as etiologic factors in stone formation apart from patients with one of the recognized predisposing systemic diseases. The intake of these crystalloids is no greater in "idiopathic" calculous patients than in the general population, either in America[7] or in England.[27] High-calcium and high-oxalate diets *per se* have been notably unsuccessful in the production of urinary calculi even in animals susceptible to spontaneous stone formation.[33] Indeed, urinary calculi appear to be relatively rare in populations where the food is abundant, varied, and includes a high intake of milk solids; Normandy, Switzerland, and the north central United States are examples.[8] The per capita consumption of milk solids in Belgium, where calculi are rare, is 46 per cent greater than in neighboring Holland, where urinary calculi are common.[28]

B. Nutritional Deficiency and Urinary Calculi

The evidence linking some form of dietary deficiency to an increased incidence of urinary calculi was noted by the earliest investigators.[31] Both uric acid and calcigerous calculi were most common among populations subsisting on monotonous rice diets, which contained a minimum of calcium and were practically free of purines and oxalates. This enigma persists to the present day.

The incidence of calcigerous urinary calculi is quite high in both children and adults of Thialand.[49] If one should choose a low-calcium, low-oxalate, low-purine diet, that of the Siamese would be ideal. Here the general term "to eat" is literally translated "to eat rice," and all food items are either rice or with rice. All the rice is milled, and none of the polishings are used as food. Only two meals are prepared per day. Fish is the only protein-rich item of the diet, but the amount consumed per day is usually small. Eggs are sold, chicken is a luxury, milk is unavailable, and red meat is forbidden. Only one-fourth of the vegetables are green or yellow, and fruit is eaten only occasionally as a snack.[24]

Experimental production of urinary calculi by deficient diets was accomplished as early as 1917.[31] The specific deficiency and the mechanism of its action remain unknown. Deficiencies of vitamin A, thiamine, certain amino acids, phosphate, magnesium, and citrate have been extensively investigated.

Vitamin A deficiency is known to produce profound changes in the morphology of epithelial cells. The metaplastic urinary epithelium observed in vitamin A deficiency was considered to produce a suitable nidus for stone formation. Clinically detectable vitamin A deficiency has not been demonstrable in American patients with urinary calculi.[30] The influence of vitamin A on renal epithelial metabolism remains to be elucidated. It may yet prove to be a factor of some importance in calculus formation. The prophylactic administration of vitamin A has received extensive clinical application in the prevention of calcigerous calculi.[26, 1] Evaluation of the effectiveness of vitamin A is clouded by the frequency with which acid ash diets and vitamin D were included in the various regimens. Both of these measures tend to increase intestinal absorption and urinary excretion of calcium. In any event, an excess of vitamin A in the diet will not invariably prevent recurrent urinary calculus formation.

Vitamin B deficiency has been somewhat empirically proposed as a cause of oxalate calculi. Interest in this has been revived with the demonstration that vitamin B_6 has transaminase activity. This suggests that a deficiency of B_6 may result in a decreased activity of a transaminase system with a resultant increase in oxalate excretion. The observation that vitamin-B_6-deficient cats regularly develop hyperoxaluria and oxalate nephrocalcinosis adds credence to the theory.[20] However, hyperoxaluria is rare in patients with calculi, even in those with congenital glycinuria,[16] and vitamin B_6-deficient cats did not form true urinary calculi. Controlled experiments relative to the role of vitamin B metabolism in human calculus formation remain to future investigators.

Reduced excretion of free amino acids, particularly glutamic acid, has been observed in patients with calculi.[39] McGeown has reported that oral DL glutamic acid will reduce the incidence of calculi in rats on a vitamin A deficient diet and in mice receiving acetazoleamine. She has suggested that glutamic acid, either alone or in some polyelectrolyte combination, may form a soluble calcium complex. She currently recommends a high-protein, low-calcium diet for patients with calcigerous urinary calculi.

The acid ash diets, once widely used in prophylaxis of urinary calculi, were either high in fat (ketogenic) or high in animal protein. The rationale was to maintain a urinary pH near five and thus to increase the solubility of calcium in the urine. Ketogenic diets were abandoned, since the patient could not tolerate them indefinitely, and urinary ammonia excretion was increased to defeat their purpose. The high-protein diets were more successful in maintaining a low urinary pH, since the titratable acidity of the urine may be increased by twofold to fourfold. The urinary inorganic sulfate derived from methionine and cystine is roughly proportional to ingested animal protein and is a fair index of protein catabolism. The increased protein content of the diet also increases the phosphate excretion and to a lesser extent the urinary calcium excretion.[38] This type of acid ash diet has found little success in the clinical application for the prevention of recurrent calculus formation. However, the experimental approach of McGeown is more in accord with the modern concept of dietary protein requirements; namely,

the need of the organism for a minimum quantity of a particular *quality* of protein, in terms of amino acid composition, rather than a specified *quantity* of protein. Such investigations may eventually lead to a better understanding of the role of nutrition in calculus formation. Individual variations in the need for relative proportions of the available amino acids may effect the propensity to calculus matrix formation quite apart from the metabolism of other dietary components or to the energy available for protein synthesis.

Magnesium exerts an influence on the solubility of calcium and oxalic acid in the urine.[23] Calculus formation in rats has been facilitated by a reduced oral intake of either magnesium[23] or phosphate.[42] Citrate concentration in the urine is less than normal in many patients with urinary calculi.[45] These deficiencies have not been established as primary factors in human calculus formation.

As science has unraveled the metabolic pathways of living cells, nutrition has increasingly appeared as a science of dietary interrelationships and less and less as a study of simple deficiencies. These subtleties are well illustrated by the investigation of the effects of replacement of rice by a cereal grain (ragi) in the poor vegetarian diets of Indian children.[32] Although the daily intake of nitrogen, carbohydrate, and lipids was essentially the same in all diets, the daily retention of nitrogen was tripled by the all-ragi diet. The mean urinary excretion of phosphorus was reduced from 155 to 118 mg./24 hrs., but the retention was increased from 117 to 135 mg./24 hrs. The mean calcium intake was increased from 259 to 1151 mg./24 hrs., and the accretion of calcium was increased from 52 to 226 mg./24 hrs., while the mean urinary excretion was reduced from 52 to 36 mg./24 hrs. by the addition of ragi to the diets. In addition to the well-known influences of vitamin D, phosphate, possibly citrate, and pH on intestinal absorption of calcium, there are other substances — lactose, lysine, and arginine —which facilitate calcium absorption and accretion.

Whatever the interrelations of nutrition and urinary concentrations may eventually prove to be, present data leaves no alternative but to include the over-all problem of calculi in the general class of deficiency diseases. Bundham Sundharagiati has justification for his prediction: "In the future, when standard of living and dietary regulations have been improved, the vesical stone in Thai children will be decreased."[49]

SUMMARY

The precise mechanisms by which uromucoid is transformed into matrix and by which it accretes organic or inorganic crystals to become an organized urinary stone are presently unknown. Many diverse pathologic states are capable of producing the conditions conducive to the operation of this mechanism. The nutritional status of the individual is an important factor in this "setting of the stage." Current evidence is overwhelmingly indicative of a dietary deficiency as the important nutritional aspect of spontaneous human calculi. The deficiency

may eventually prove to be relative and multiple rather than absolute and singular. On the other hand, there is no evidence that dietary surfeit without nutritional deficiency is ever an important factor in human stone formation.

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